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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/665,976	09/20/2000	Lawrence W. Stanton	SCIOS.014A	8472

10/21/2002

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EXAMINER	
SOUAYA, JEHANNE E	
ART UNIT	**PAPER NUMBER**
1634	14

DATE MAILED: 10/21/2002

below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/665,976	Stanton et al
Examiner	**Art Unit**
Jehanne Souaya	1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jul 17, 2002* .

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-7 and 30-33* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☒ Claim(s) *31* is/are allowed.

6) ☒ Claim(s) *1-7, 30, 32, and 33* is/are rejected.

7) ☒ Claim(s) *1* is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Currently, claims 1-7 and newly added claims 30-34 are pending in the instant application. All the amendments and arguments have been thoroughly reviewed but are deemed insufficient to place this application in condition for allowance. Any rejections not reiterated are hereby withdrawn. The following rejections are either newly applied (necessitated by amendment) or are reiterated. They constitute the complete set being presently applied to the instant Application. Response to Applicant's arguments follow. This action is FINAL.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Maintained Rejections

Claim Rejections - 35 USC § 112

3. Claims 1-7 and newly added claims 30, and 32-33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claim 1, in sections a, c,d,e, and f, and newly added claims 30 and 32 are indefinite over the phrase "at least about" because the metes and bounds of the invention are not clear. As the CAFC noted, and affirmed, regarding the district court determination of this phrase in Amgen Inc. v. Chugai Pharmaceutical Co. Ltd. (CA FC) 18 USPQ2d 1016 at page 1031 "the court held the "at least about" claims to be invalid for indefiniteness."

Response to Arguments

The response asserts that the amendment to claim 1 no longer recites "at least about", however, upon further review, the claims still recite this language.

B) Claim 1, in section c, is indefinite in the recitation of "or inactivated variant" as it is unclear if the "the inactivated variant" refers to a polypeptide where the transmembrane domain is inactivated or whether any portion of the polypeptide could be inactivated.

Response to Arguments

The response asserts that the amendment to claim 1 no longer recites "or inactivated variant", however, upon further review, the claims still recite this language.

Claim Rejections - 35 USC § 102

4. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Accession number AA891470 (June 16, 1998).

Section g is drawn to the complement of sections e or f, which are drawn to a polynucleotide encoding at least about 50 contiguous amino acids from amino acids 25 to 214 and 25-236 of SEQ ID NO 2. The complement of the nucleic acid of AA891470 encodes amino acids 157 to 224 (67 amino acids) of SEQ ID NO 1 (positions 131-331 of AA891470).

Response to Arguments

5. The response traverses that AA891470 only describes portions of the claimed polynucleotides and that the claims now contain the additional limitation of the ability of the complement of such polynucleotides to detect by microarray analysis a polynucleotide that is differentially expressed. These arguments have been thoroughly reviewed but were found unpersuasive. Firstly, with regard to sections e and f of claim 1, the claims only recite a polynucleotide that codes for a portion of SEQ ID NO 1 ("at least about 50 amino acids") which is taught by AA891470. Secondly, the recitation of "detects by microarray analysis" does not distinguish the claimed polynucleotides from the polynucleotide taught by AA891470 due to the high degree of complementarity between the full length of AA891470 and SEQ ID NO 2, AA891470 only contains 2 mismatches between positions 1 to 446 (it is only 459 nucleotides long) and contains a large region - 200 nucleotides- of complete complementarity (position 131-331 of AA891470) to SEQ ID NO 2. Therefore AA891470 would be able to hybridize to SEQ ID NO 2.

Double Patenting

The obviousness type double patenting rejection made in the previous office action is maintained as the claims are not presently in condition for allowance.

New Grounds of Rejection and Objection

Claim Objections

6. Claim 1 is objected to because of the following informalities: the claim recites the phrase "cardial disease model" in a number of different sections, however the specification provides no support for the recitation of "cardial disease model". The word 'cardial' appears to be misspelled This objection can be easily overcome by correcting the misspelling. Appropriate correction is required.

Enablement

7. Claims 1-2, 5-7, and newly added claims 30 and 32-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated nucleic acid molecule comprising a polynucleotide encoding a polypeptide comprising SEQ ID NO 1, an isolated nucleic acid molecule encoding amino acids 25 to 236 of SEQ ID NO 1, an isolated nucleic acid molecule comprising the sequence of SEQ ID NO 2, the complement thereof, and a vector or host cell comprising such, an isolated nucleic acid comprising a polynucleotide encoding a polypeptide having at least 90% sequence identity with SEQ ID NO 1, wherein the complement of said polynucleotide detects, by microarray analysis, a polynucleotide that is differentially expressed by about 1.8 fold in an in vivo or in vitro cardiac disease model, an isolated nucleic acid comprising a polynucleotide encoding a polypeptide having at least 90% sequence identity with amino acids 25-214 SEQ ID NO 1, wherein the complement of said polynucleotide detects, by microarray analysis, a polynucleotide that is differentially expressed

by about 1.8 fold in an in vivo or in vitro cardiac disease model; does not reasonably provide enablement for a nucleic acid molecule comprising: a polynucleotide encoding a polypeptide having at least 90% sequence identity with SEQ ID NO 1, wherein the complement of said polynucleotide detects, by microarray analysis, a polynucleotide that is differentially expressed by at least about 1.8 fold in an in vivo or in vitro cardiac disease model; a polynucleotide encoding a polypeptide having at least 90% sequence identity with amino acids 25-214 of SEQ ID NO 1, wherein the complement of said polynucleotide detects, by microarray analysis, a polynucleotide that is differentially expressed by at least about 1.8 fold in an in vivo or in vitro cardiac disease model; a polynucleotide encoding a polypeptide having at least 90% sequence identity with amino acids 25-236 of SEQ ID NO 1; a transmembrane domain deleted or inactivated variant of a polynucleotide encoding amino acids 25 to 236 of SEQ ID NO 1 wherein the complement of said polynucleotide detects by microarray analysis, a polynucleotide that is differentially expressed about or at least about 1.8 fold in an in vivo or in vitro cardiac disease model; a polynucleotide encoding at least about 50 contiguous amino acids from amino acids 25-214 of SEQ ID NO 1, wherein the complement of said polynucleotide detects, by microarray analysis, a polynucleotide that is differentially expressed by at least about 1.8 fold in an in vivo or in vitro cardiac disease model; a polynucleotide encoding at least about 50 contiguous amino acids from amino acids 25-236 of SEQ ID NO 1 wherein the complement of said polynucleotide detects, by microarray analysis, a polynucleotide that is differentially expressed by at least about 1.8 fold in an in vivo or in vitro cardiac disease model; complements thereof, a polynucleotide

encoding a polypeptide comprising amino acids 25 to 214 of SEQ ID NO: 1 which depend from such, or vectors and host cells comprising such; or to an isolated polynucleotide encoding a polypeptide comprising a native mammalian homologue having at least 90% amino acid identity to a portion of SEQ ID NO 1 wherein the complement of said polynucleotide detects, by microarray analysis, a polynucleotide that is differentially expressed by about or at least about 1.8 fold in an in vivo or in vitro cardiac disease model. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The claims as written broadly encompass mutants, variants, and homologs of SEQ ID NOS 1 and 2 from any source. The specification teaches the polypeptide of SEQ ID NO 1 and the polynucleotide of SEQ ID NO 2. The specification teaches that using micro array analysis, the expression level of the gene corresponding to clone P00188_D12 (SEQ ID NO 2) was about 2 fold down regulated in a myocardial infarction rat model, 2.5 fold down regulated in a cardiac hypertrophy rat model, and about 2 fold up regulated in a viral myocarditis mouse model (p. 65). The specification teaches that the deduced amino acid sequence was determined (SEQ ID NO 1) and the open reading frame "contains 236 amino acid residues, of which approximately the first 24 residues show characteristics of a putative signal sequence and a probable membrane spanning region at positions 215-235".

Polynucleotides encompassed by the claims, such as: a polynucleotide encoding a polypeptide having 90% sequence identity with amino acids 25 to 236 of SEQ ID NO:1, a

transmembrane domain deleted or inactivated variant of the polynucleotide encoding amino acids 25 to 236 of SEQ ID NO 1, or polynucleotides that encode at least 50 contiguous amino acids from amino acids 25 to 214 or 236 of SEQ ID NO 1, or complements thereof or polynucleotides that hybridize to the region of SEQ ID NO 2 that codes for SEQ ID NO 1 under condition of high stringency (newly added claims 32 and 33); include mutants, variants, and homologs of SEQ ID NOS 1 and 2, resulting from missense, frameshift and truncation mutations, from any source, which have not been taught in either the specification or the art. The recitation of "wherein the complement of said polynucleotide detects, by microarray analysis, a polynucleotide that is differentially expressed by at least about 1.8 fold..." does not further limit claims in sections where it is recited, to enable the claimed polynucleotides, because such recitation only comprises a lower level of differential expression "about 1.8", but does not exclude polynucleotide sequences that have been differentially expressed by 4 fold, 10 fold, or higher, which have not been taught or described by the specification.

With regard to claim 1d and claim 30, a recitation of "wherein the complement of said polynucleotide detects, by microarray analysis, a polynucleotide that is differentially expressed by about 1.8 fold..." would not enable the claimed polynucleotides, because, with respect to claim 1d, although the specification teaches at page 38, that amino acids 215 to 235 "have been tentatively identified as membrane spanning segments", the specification has not taught that this "tentative" transmembrane domain is essential for the activity of the polypeptide of SEQ ID NO 1, and if it is, the specification has not taught which amino acid mutations (ie: substitutions,

deletions or insertions) would lead to an "inactivated" transmembrane domain or an "inactivated" protein. With respect to claim 30, the recitation of "having at least 90% amino acid sequence identity *to* SEQ ID NO 1", encompasses a polynucleotide that encodes as few as 9 out of 10 total amino acids of SEQ ID NO 1, with an unlimited number of nucleotides on either side, that is, any homologue that is only 90% identical to any portion of SEQ ID NO 1 and which also detects a polynucleotide that is differentially expressed by about 1.8 fold in a cardiac disease model. However, the specification does not teach of any cardiac disease model where a polynucleotide encoding an inactivated form or homologue of only a small portion of SEQ ID NO 1 is differentially expressed by about 1.8 fold. The skilled artisan would be unable to envision the detailed chemical structure of such polynucleotides, regardless of the complexity or simplicity of the method of isolation.

With regard to claim 2, at page 38, the specification teaches that amino acids 215 to 235 "have been tentatively identified as membrane spanning segments". The specification teaches that the present invention includes amino acid sequence variants of the native rat polypeptide of SEQ ID NO 1, or its analogs *in any other animal*, and include sequences with more than one amino acid substitutions, or polypeptides in which the membrane spanning region or regions are deleted or inactivated. Therefore, the specification teaches that the recitation encompassed by "a polynucleotide encoding a polypeptide comprising amino acids 25 to 214 of SEQ ID NO 1" includes sequences with more than one amino acid substitutions, or polypeptides in which the membrane spanning region or regions are deleted or inactivated.

The specification does not teach the function of the polypeptide of SEQ ID NO 1, nor how the biological activity or expression of this polypeptide is associated with any of the animal models taught in the specification. The specification has not demonstrated which amino acids or domains of the polypeptide of SEQ ID NO 1 are necessary for the activity of the polypeptide. The specification has not taught any biological assays that the skilled artisan could use to determine amino acids or domains of the polypeptide of SEQ ID NO 1 that are responsible or necessary for its biological activity. While the specification teaches at page 38, that amino acids 215 to 235 "have been tentatively identified as membrane spanning segments", the specification has not taught that this "tentative" transmembrane domain is essential for the activity of the polypeptide of SEQ ID NO 1, and if it is, the specification has not taught which amino acid mutations (ie: substitutions, deletions or insertions) would lead to an "inactivated" transmembrane domain or an "inactivated" protein. Neither the specification nor the art teach the specific biological activity of the polypeptide encoded by SEQ ID NO 2, so that the skilled artisan might be able to predict which changes would result in polypeptides with either retained or altered biological activity. It is known for nucleic acids as well as proteins that even a single nucleotide or amino acid change or mutation can destroy or alter the function of a biomolecule in many instances, albeit not in all cases (see Proudfoot et al, Journal of Biological Chemistry, vol. 271, pp 2599-2603, which teaches that extension of recombinant human RANTES by a single residue [Met-RANTES] at the amino terminus was sufficient to produce a potent and selective

antagonist - see abstract). The effect of these changes are largely unpredictable as to which ones have a significant effect verses not.

A correlation between mutants, variant and homologs encompassed by the claims and a specific biological activity is clearly unpredictable in light of the lack of guidance from the specification and the state of the art with regard to the specific biological function or activity of the polypeptide encoded by SEQ ID NO: 2. Since neither the specification nor the art teach the specific biological function or activity of the polypeptide of SEQ ID NO 1, nor how the skilled artisan could modify the polypeptide of SEQ ID NO 1 to obtain a polypeptide with either retained or modified activity, the skilled artisan would be required to perform undue experimentation to make or use the polynucleotides that encode biologically active or altered polypeptides encompassed by the broadly claimed invention. To practice the invention as broadly as it is claimed, the skilled artisan would first have to determine the function or specific biological activity of the polypeptide of SEQ ID NO 1. The skilled artisan would then have to develop an assay by which to measure biological activity and would have to determine what amino acid residues were important for such specific activity, and then would have to determine which amino acids could be modified to either retain biological activity or to result in a protein with altered activity. Given that the art teaches that a single amino acid change can alter the function of a biomolecule and that some of these changes are unpredictable, and given that the specification does not a) teach the function of the polypeptide of SEQ ID NO 1, and b) provide any guidance as to an assay that the skilled artisan could use to measure the biological activity of

the claimed polypeptide, such analyses would require trial and error, thus constituting undue experimentation. It is noted that because the skilled artisan would be required to perform undue experimentation to make and use the polynucleotides of claims 1 and 2, undue experimentation would also be required to make or use the complements of these nucleic acids and vectors or host cells comprising these polynucleotides.

Response to Arguments

The response traverses the rejection. With regard to the assertions regarding a specific or substantial utility of a polynucleotide encoding a polypeptide with 90% identity to SEQ ID NO 1, the claimed polynucleotides were not rejected under 35 USC 101, but under 35 USC 112/first paragraph. The response asserts further asserts that applicants have also amended to recite polynucleotides whose complement "detects, by microarray analysis, a polynucleotide that is differentially expressed by at least about 1.8 fold in an in vivo or in vitro cardiac disease model". This argument has been thoroughly reviewed but was not found persuasive, because, as noted above, the specification only teaches cardiac disease models that showed "2 fold, 2.5 fold, or 1.7 fold" differential expression, whereas the recitation of "at least about" does not exclude 4 fold or 10 fold expression. The specification, however, has not shown a predictable correlation between the claimed polynucleotides and expression above 2.5 fold. With regard to applicants assertion that any polynucleotide species falling within the scope of claim 1 would possess at least one specific and substantial utility, as noted earlier the claimed polynucleotides were not rejected

under 35USC 101, but under 35 USC 112/first paragraph, which requires that the full scope of the claimed invention be enabled by the specification's disclosure.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claim 30 is rejected under 35 U.S.C. 103(a) as being unpatentable over Accession number AA891470 (June 16, 1998).

Claim 30 is drawn to an isolated polynucleotide encoding a polypeptide comprising a native mammalian homologue having at least 90% amino acid identity to SEQ ID NO: 1. The complement of Accession number AA891470 is almost identical to a portion of SEQ ID NO 2,

AA891470 only contains 2 mismatches between positions 1 to 446 (it is only 459 nucleotides long) and contains a large region - 200 nucleotides- of complete complementarity (position 131-331 of AA891470) to SEQ ID NO 2. Taking into account the number of mismatches that AA891470 has with positions 382 to 840 of SEQ ID NO 2 (15) such would code for at most 7 amino acid changes, which would result in a protein which is 95% identical to SEQ ID NO 1. It is noted that the recitation of "90% amino acid identity *to* SEQ ID NO: 1" encompasses identity to only a portion of SEQ ID NO 1 (whereas the recitation of "with SEQ ID NO 1" would mean the full length of SEQ ID NO 1). The recitation of "detects by microarray analysis" does not distinguish the claimed polynucleotides from the polynucleotide taught by AA891470 due to the high degree of complementarity between the full length of AA891470 and SEQ ID NO 2, AA891470 only contains 2 mismatches between positions 1 to 446 (it is only 459 nucleotides long) and contains a large region - 200 nucleotides- of complete complementarity (position 131-331 of AA891470) to SEQ ID NO 2. Therefore AA891470 would be able to hybridize to SEQ ID NO 2. Although accession number AA891470 is the complement of the isolated polynucleotide of claim 30, it would have been prima facie obvious to one of ordinary skill in the art to synthesize the complement of AA891470 (thus the polynucleotide of claim 30) for the purposes of detecting AA891470 in a hybridization assay.

Conclusion

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

11. Claim 31 is allowable.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Souaya whose telephone number is (703)308-6565. The examiner can normally be reached Monday-Friday from 9:00 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax phone number for this Group is (703) 305-3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jehanne Souaya

Jehanne Souaya
Patent examiner
Art Unit 1634
October 15, 2002

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600